

**Notice of Allowability**

Application No.

10/729,427

Applicant(s)

TRACEY ET AL.

Examiner

Art Unit

Michel Graffeo

1614

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--**

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to Amendment after final filed 19 May 2006.
2. ☒ The allowed claim(s) is/are 1,4-19,23 and 24.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some\* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\* Certified copies not received: \_\_\_\_\_.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

**THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.**

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date \_\_\_\_\_.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date \_\_\_\_\_.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

*\* Drawings are approved by Examiner*

**Attachment(s)**

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO/SB/08),  
Paper No./Mail Date \_\_\_\_\_
4. ☐ Examiner's Comment Regarding Requirement for Deposit  
of Biological Material
5. ☐ Notice of Informal Patent Application
6. ☐ Interview Summary (PTO-413),  
Paper No./Mail Date \_\_\_\_\_
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other \_\_\_\_\_

### **EXAMINER'S AMENDMENT**

An extension of time under 37 CFR 1.136(a) is required in order to make an examiner's amendment which places this application in condition for allowance. During a telephone conversation conducted on 4 January 2007, Counselor Davis requested an extension of time for FIVE MONTH(S) and authorized the Director to charge Deposit Account No. 08-0380 the required fee of \$ 2160.00 for this extension and authorized the following examiner's amendment. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

Delete the previous Abstract. The Abstract has been replaced to read as follows:

### **ABSTRACT OF THE DISCLOSURE**

Methods for inhibiting an inflammatory cytokine cascade in a patient are provided. The methods are directed to treating the patient with a cholinergic agonist in an amount sufficient to inhibit the inflammatory cytokine cascade, wherein the cholinergic agonist is selective for an  $\alpha 7$  nicotinic receptor.

Claims 1,4-19 and 24 are allowed. By this Amendment, Claim 1 is amended to that which is shown below, to limit the list of treatable indications. Claims 2-3, 20-23 and 25-55 are cancelled. The listing of claims below will replace all prior versions and listings of claims in the application:

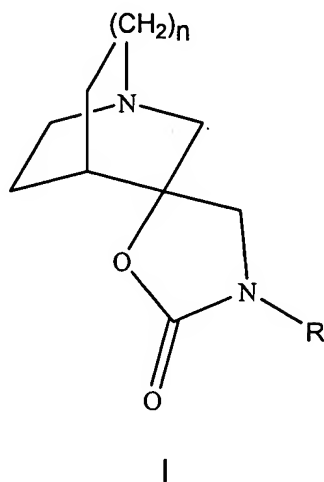
1. (Currently Amended) A method of treating a patient suffering from an inflammatory condition, comprising treating said patient with a therapeutically effective amount of a cholinergic agonist selective for an  $\alpha 7$  nicotinic receptor, wherein said condition is selected from the group consisting of peritonitis, sepsis, endotoxic shock, adult respiratory distress syndrome, chronic obstructive pulmonary disease, rheumatoid arthritis, systemic lupus erythematosus, allograft rejection, asthma, graft-versus-host-disease, congestive heart failure and cystic fibrosis.

2-3. (Cancelled)

4. (Original) The method of claim 1, wherein the cholinergic agonist is selected

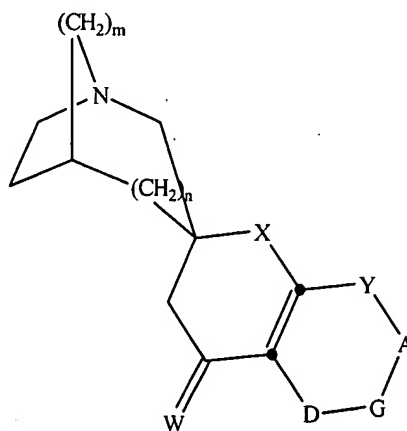
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from the group consisting of a quaternary analog of cocaine; (1-aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid 1-(2-fluorophenyl)-ethyl ester; a compound of formula I:



wherein, R represents hydrogen or methyl, and

n represents 0 or 1; a pharmaceutically acceptable salt of a compound of formula I; a compound of formula II:



II

wherein:

m is 1 or 2,

n is 0 or 1,

Y is CH, N or NO,

X is oxygen or sulfur,

W is oxygen, H<sub>2</sub> or F<sub>2</sub>,

A is N or C(R<sup>2</sup>),

G is N or C(R<sup>3</sup>),

D is N or C(R<sup>4</sup>),

with the proviso that no more than one of A, G and D is nitrogen but at least one of Y, A, G and D is nitrogen or NO,

R<sup>1</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl,

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, heteroaryl, OH, OC<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>R<sup>1</sup>, -CN, -NO<sub>2</sub>, -NR<sup>5</sup>R<sup>6</sup>, -CF<sub>3</sub> or -OSO<sub>2</sub>CF<sub>3</sub>, or R<sup>2</sup> and R<sup>3</sup>, R<sup>3</sup> and R<sup>4</sup>, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substituents: independently hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, heteroaryl, OH, OC<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>R<sup>1</sup>, -CN, -NO<sub>2</sub>, -NR<sup>5</sup>R<sup>6</sup>, -CF<sub>3</sub> or -OSO<sub>2</sub>CF<sub>3</sub>;

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$R^5$  and  $R^6$  are independently hydrogen,  $C_1$ - $C_4$  alkyl,  $C(O)R^7$ ,  $C(O)NHR^8$ ,  $C(O)OR^9$ ,  $SO_2R^{10}$  or may together be  $(CH_2)_jQ(CH_2)_k$  where Q is O, S,  $NR^{11}$ ,

or a bond,

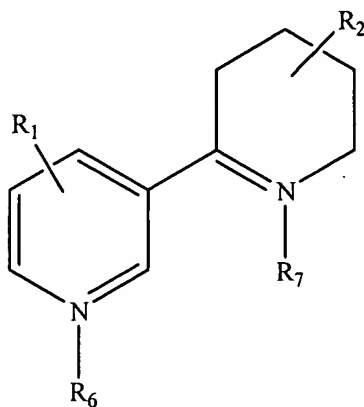
j is 2 to 7,

k is 0 to 2,

$R^7$ ,  $R^8$ ,  $R^9$ ,  $R^{10}$  and  $R^{11}$  are independently  $C_1$ - $C_4$  alkyl, aryl, or heteroaryl, or

an enantiomer thereof; a pharmaceutically acceptable salt of a compound of

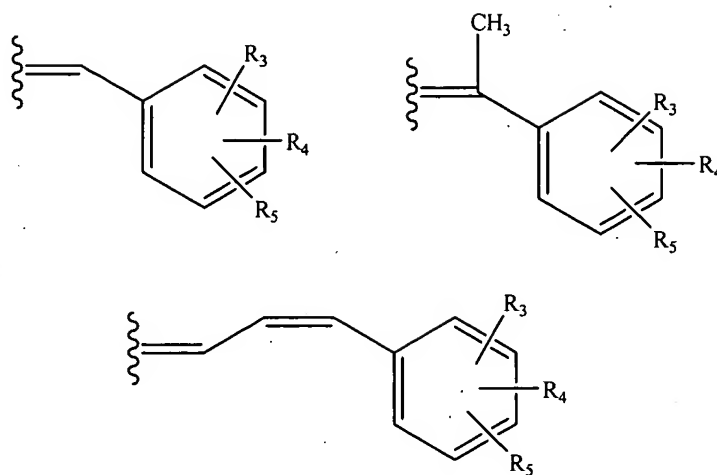
formula II; a compound of formula III:



III

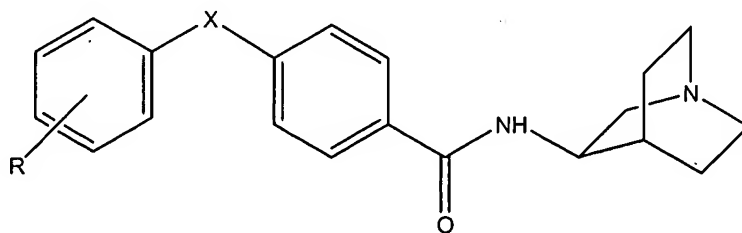
wherein  $R_1$ ,  $R_6$  and  $R_7$  are hydrogen or  $C_1$ - $C_4$  alkyl, and  $R_2$  is selected from a group of

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and

wherein,  $R_3$ ,  $R_4$  and  $R_5$  are selected from the group consisting of hydrogen,  $\text{C}_1\text{-C}_4$  alkyl optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls,  $\text{C}_1\text{-C}_6$  alkoxy optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls; carboalkoxy having 1 to 4 carbons in the alkoxy, amino, amido having 1 to 4 carbons in the acyl, cyano, and N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, halo, hydroxyl or nitro; and a compound of formula IV:



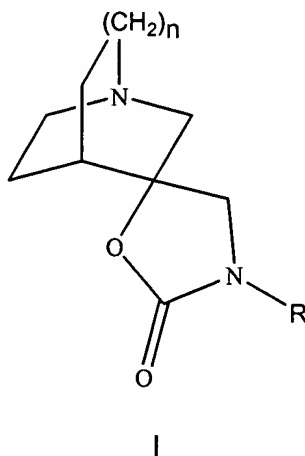
IV

wherein  $X$  is O or S, and  $R$  is selected from the group consisting of H,  $\text{OR}_1$ ,

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NHC(O)R<sub>1</sub>, and a halogen, wherein R<sub>1</sub> is a C<sub>1</sub>-C<sub>4</sub> alkyl.

5. (Original) The method of claim 1, wherein the cholinergic agonist is a compound of formula I:



wherein, R represents hydrogen or methyl, and

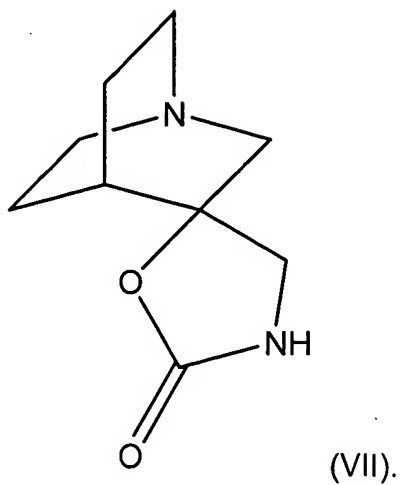
n represents 0 or 1;

or a pharmaceutically acceptable salt thereof.

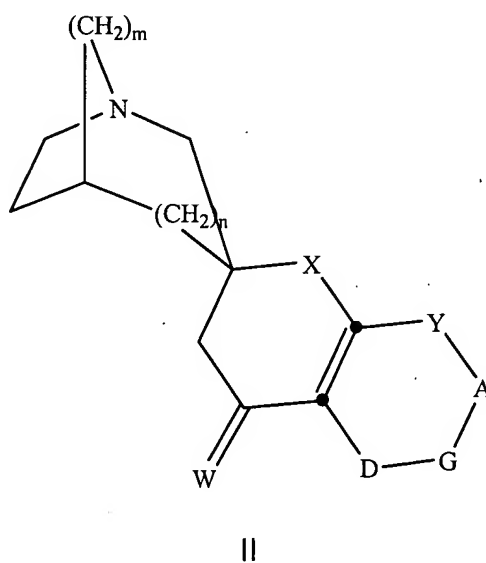
6. (Original) The method of claim 5, wherein the cholinergic agonist is (-)-spiro[1-azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one]



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7. (Original) The method of claim 1, wherein the cholinergic agonist is a compound of formula II:



wherein:

m is 1 or 2;

n is 0 or 1;

Y is CH, N or NO;

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X is oxygen or sulfur;

W is oxygen, H<sub>2</sub> or F<sub>2</sub>;A is N or C(R<sup>2</sup>);G is N or C(R<sup>3</sup>);D is N or C(R<sup>4</sup>);

with the proviso that no more than one of A, G and D is nitrogen but at least one of Y, A, G and D is nitrogen or NO;

R<sup>1</sup> is hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl;

R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are independently hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, heteroaryl, OH, OC<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>R<sub>1</sub>, -CN, -NO<sub>2</sub>, -NR<sub>5</sub>R<sub>6</sub>, -CF<sub>3</sub> or -OSO<sub>2</sub>CF<sub>3</sub>, or R<sup>2</sup> and R<sup>3</sup>, R<sup>3</sup> and R<sup>4</sup>, respectively, may together form another six membered aromatic or heteroaromatic ring sharing A and G, or G and D, respectively, containing between zero and two nitrogen atoms, and substituted with one to two of the following substituents: independently hydrogen, halogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>2</sub>-C<sub>4</sub> alkenyl, C<sub>2</sub>-C<sub>4</sub> alkynyl, aryl, heteroaryl, OH, OC<sub>1</sub>-C<sub>4</sub> alkyl, CO<sub>2</sub>R<sup>1</sup>, -CN, -NO<sub>2</sub>, -NR<sup>5</sup>R<sup>6</sup>, -CF<sub>3</sub> or -OSO<sub>2</sub>CF<sub>3</sub>;

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, C(O)R<sup>7</sup>, C(O)NHR<sup>8</sup>, C(O)OR<sup>9</sup>, SO<sub>2</sub>R<sup>10</sup> or may together be (CH<sub>2</sub>)<sub>j</sub>Q(CH<sub>2</sub>)<sub>k</sub> where Q is O, S, NR<sup>11</sup>,

or a bond;

j is 2 to 7;

k is 0 to 2;

R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup> and R<sup>11</sup> are independently C<sub>1</sub>-C<sub>4</sub> alkyl, aryl, or heteroaryl,

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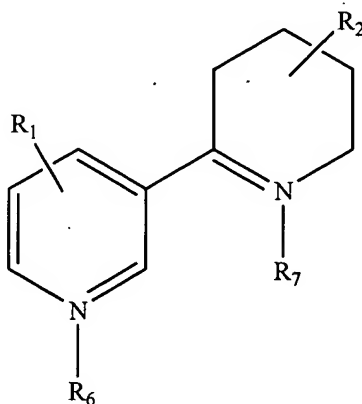
or an enantiomer thereof,

or a pharmaceutically acceptable salts thereof.

8. (Original) The method of claim 7, wherein the cholinergic agonist is a compound of formula II wherein m is 1; n is 0; p is 0; x is oxygen; A is C(R<sup>2</sup>); G is C(R<sup>3</sup>); and D is C(R<sup>4</sup>).

9. (Original) The method of claim 7, wherein the cholinergic agonist is 5'-phenylspiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo[2,3-b]pyridin].

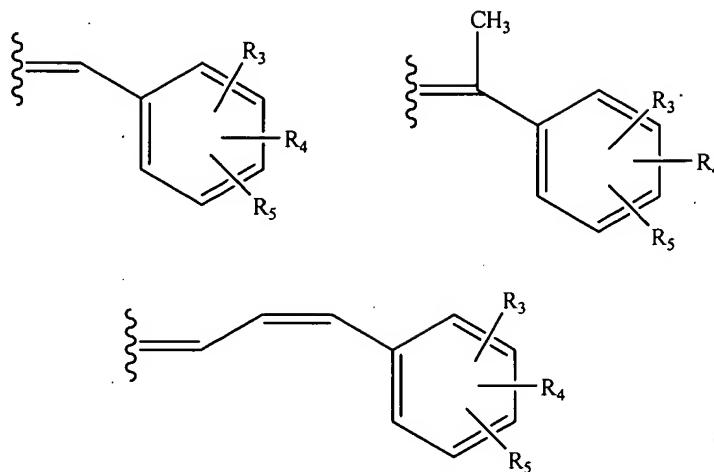
10. (Original) The method of claim 1, wherein the cholinergic agonist is a compound of formula III:



(III)

wherein R<sub>1</sub>, R<sub>6</sub> and R<sub>7</sub> are hydrogen or C<sub>1</sub>-C<sub>4</sub> alkyl; and R<sub>2</sub> is selected from a group of

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and wherein, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are selected from the group consisting of hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, C<sub>1</sub>-C<sub>6</sub> alkoxy optionally substituted with N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, carboalkoxy having 1 to 4 carbons in the alkoxy, amino, amido having 1 to 4 carbons in the acyl, cyano, and N,N-dialkylamino having 1 to 4 carbons in each of the alkyls, halo, hydroxyl or nitro.

11. (Original) The method of claim 10, wherein the cholinergic agonist is a compound of formula III, wherein R<sub>2</sub> is attached to the 3-position of the tetrahydropyridine ring, and further wherein R<sub>3</sub>, which is attached to the 4- or the 2- position of the phenyl ring, is selected from the group consisting of amino, hydroxyl, chloro, cyano, dimethylamino, methyl, methoxy, acetylamino, acetoxyl, and nitro.

12. (Original) The method of claim 10, wherein the cholinergic agonist is a compound selected from the group consisting of formula III, wherein R<sub>3</sub> is hydroxyl, and wherein

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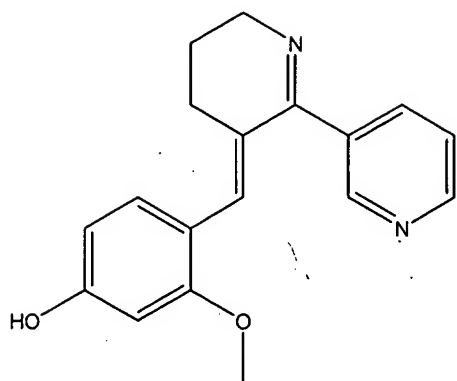
R<sub>1</sub>, R<sub>4</sub>, and R<sub>5</sub> are hydrogen; formula III, wherein R<sub>3</sub> is acetylamino and wherein R<sub>1</sub>, R<sub>4</sub>, and R<sub>5</sub> are hydrogen; formula III, wherein R<sub>3</sub> is acetoxy and wherein R<sub>1</sub>, R<sub>4</sub>, and R<sub>5</sub> are hydrogen; formula III, wherein R<sub>3</sub> is methoxy, and wherein R<sub>1</sub>, R<sub>4</sub>, and R<sub>5</sub> are hydrogen; formula III, wherein R<sub>3</sub> is methoxy and wherein R<sub>1</sub> and R<sub>4</sub> are hydrogen, and further wherein R<sub>3</sub> is attached to the 2-position of the phenyl ring, and R<sub>5</sub>, which is attached to the 4-position of the phenyl ring, is methoxy or hydroxy.

13. (Original) The method of claim 10, wherein the cholinergic agonist is selected from the group consisting of 3-2,4-dimethoxybenzylidene anabaseine (DMXB-A), 3-(4-hydroxybenzylidene)anabaseine, 3-(4-methoxybenzylidene)anabaseine, 3-(4-aminobenzylidene)anabaseine, 3-(4-hydroxy-2-methoxybenzylidene)anabaseine, 3-(4-methoxy-2-hydroxybenzylidene)anabaseine, trans-3-cinnamylidene anabaseine, trans-3-(2-methoxy-cinnamylidene)anabaseine and trans-3-(4-methoxycinnamylidene)anabaseine.

14. (Previously Presented) The method of claim 10, wherein the cholinergic agonist is

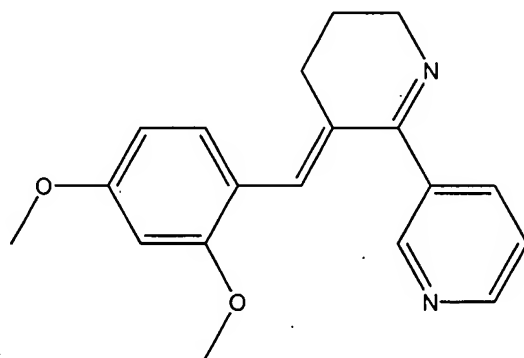
3-(4-hydroxy-2-methoxybenzylidene) anabaseine

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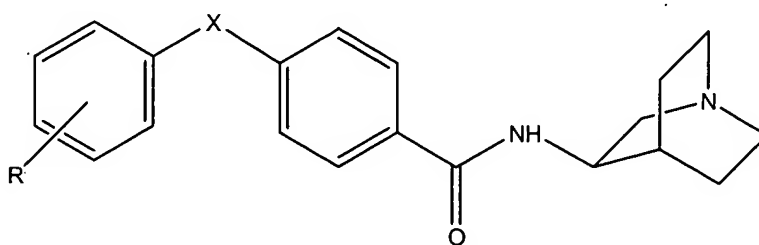
(VI).

15. (Original) The method of claim 10, wherein the cholinergic agonist is 3-(2,4-dimethoxybenzylidene)anabaseine.



(V).

16. (Original) The method of claim 1, wherein the cholinergic agonist is a compound of formula IV:



IV

wherein X is O or S; and

R is selected from the group consisting of H, OR<sub>1</sub>, NHC(O)R<sub>1</sub>, and a halogen, wherein R<sub>1</sub> is a C<sub>1</sub>-C<sub>4</sub> alkyl.

17. (Original) The method of claim 15, wherein the cholinergic agonist is selected from a group consisting of N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-hydroxyphenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(4-acetamidophenoxy)benzamide, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide, and N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(3-chlorophenylsulphonyl)benzamide.

18. (Original) The method of claim 15, wherein the cholinergic agonist is N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-(phenylsulfanyl)benzamide.

19. (Original) The method of claim 1, wherein the cholinergic agonist is cocaine methiodide.

20. (Cancelled)

21. (Cancelled)

- 22. (Cancelled)
- 23. (Cancelled)
- 24. (Original) The method of claim 1, wherein the condition is sepsis.

### ***Reasons for Allowance***

The following is an examiner's statement of reasons for allowance: the instant claims have been amended, the scope of which the Examiner believes is now currently reflective of and commensurate with the invention as enabled in the specification. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michel Graffeo whose telephone number is 571-272-8505. The examiner can normally be reached on 9am to 5:30pm Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.




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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4 January 2007

MG

 1/5/07  
ARDIN H. MARSCHEL  
SUPERVISORY PATENT EXAMINER